**Prognostic Value of Left Atrial Function in Dogs with Chronic Mitral Valvular Heart Disease**


**Background:** A strong correlation between left atrial (LA) dysfunction and the severity of cardiac disease has been described in human patients with various cardiac diseases. The role of LA dysfunction in dogs with chronic mitral valvular heart disease (CMVHD) has not been addressed.

**Objectives:** To investigate the correlation between LA function and the prognosis of dogs with CMVHD.

**Animals:** Thirty-eight client-owned dogs with CMVHD.

**Methods:** Prospective clinical cohort study. Dogs were divided into 2 groups (survivors and nonsurvivors) based on the onset of cardiac-related death within 1 year. Physical examination and echocardiographic variables were compared between the groups. For the assessment of the comparative accuracy in identifying patients with cardiac-related death, receiver operating characteristic (ROC) curves and multivariate logistic analysis were used.

**Results:** The highest accuracy was obtained for the LA active fractional area change (LA-FAC_{act}), with an area under the ROC curve (AUC) of 0.95, followed by the left atrial to aortic root ratio (LA/Ao), with an AUC of 0.94; peak early diastolic mitral inflow velocity (E), with an AUC of 0.85; and LA total fractional area change (LA-FAC_{total}), with an AUC of 0.85. In the multivariate logistic regression analysis, LA-FAC_{act} emerged as the only independent correlate of cardiac-related death within 1 year (odds ratio = 1.401, \( P = .002 \)).

**Conclusions and Clinical Importance:** Regarding both the size and function, the LA has a strong correlation with the prognosis of dogs with CMVHD. The most significant independent predictor of mortality in this study was LA-FAC_{act}.

**Key words:** Cardiac-related death; Dog; Echocardiography; Left atrial emptying fraction.

**Abbreviations:**
- late diastolic mitral inflow velocity
- late diastolic velocity of the septal mitral annulus
- area under the receiver operating characteristic curve
- confidence interval
- chronic mitral valvular heart disease
- early diastolic velocity of the septal mitral annulus
- peak early diastolic mitral inflow velocity
- fractional shortening
- left atrial to aortic root ratio
- left atrial active fractional area change
- left atrial passive fractional area change
- left atrial total fractional area change
- left atrial
- maximum area of the left atrium at ventricular end-systole
- minimum area of the left atrium at ventricular end-diastole
- left atrium at onset of the P wave on the ECG
- percent increase in left ventricular diameter in diastole
- left ventricular diameter in diastole
- percent increase in left ventricular diameter in systole
- left ventricular diameter in systole
- left ventricular
- mitral regurgitation
- receiver operating characteristic

**A** chronic mitral valvular heart disease (CMVHD) is the most common heart disease in dogs. This disease is caused by progressive myxomatous degeneration of the mitral valve, leading to incomplete coaptation of the leaflets and valvular regurgitation.\(^1,2\) The reported prevalence of this disease in small dogs ranges from 14% to over 40%, depending on the breed.\(^3–5\) Although most dogs with CMVHD remain asymptomatic for years or even for life,\(^6–9\) the progression of mitral regurgitation (MR) can cause severe congestive heart failure, leading to death in some dogs.

Predicting the onset of congestive heart failure or cardiac-related death is of clinical importance. To date, many studies have investigated the prognostic factors for survival or disease worsening in dogs with CMVHD.\(^9–12\) The high prognostic value of the degree of left atrial (LA) dilatation has been demonstrated in dogs with CMVHD.\(^10–12\) Chronic and hemodynamically significant MR results in volume overload, which is first characterized by LA enlargement. Echocardiography can be used to measure LA size noninvasively; traditionally, LA size is measured by using linear M-mode or two-dimensional (2D) methods. The left atrial to aortic root ratio (LA/Ao) determined from the right parasternal short axis view is the most commonly used method for measuring LA size.\(^12\)
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Materials and Methods

Classification

Dogs were divided into 2 groups for statistical analysis based on whether they survived for more than 1 year after the first echocardiographic examination (Group A, “survivors”) or experienced cardiac-related death within 1 year after the first echocardiographic examination (Group B, “nonsurvivors”). Cardiac-related death was defined as death occurring because of progression of clinical signs of heart failure without any other identifiable cause of death.

Conventional Echocardiography and Doppler Examination

Conventional 2D and M-mode echocardiographic and Doppler examinations were performed by an experienced veterinarian (KN) with an ultrasound unit (HI VISION Preirus®) equipped with a 3–7 MHz phased array sector probe (EUP-S52®) in all dogs. Dogs were unsedated and gently restrained in left and right lateral recumbency during the examination. Measurements were obtained using the 2D-guided M-mode with concomitant ECG registration for the ventricles according to the guidelines of the American Society of Echocardiography.20 The LA/Ao was obtained from the right parasternal short axis 2D view as previously described.21 The LV diameter in diastole (LVIDd) and LV diameter in systole (LVIDs) were measured from the M-mode echocardiogram from the right parasternal short axis 2D view.21 M-mode values were used to derive the fractional shortening (FS) and the percent increase in LVIDd (LVIDd inc%) and LVIDs (LVIDs inc%) according to the following equation22: % increase = 100 × (observed dimension – expected normal dimension)/expected normal dimension. Expected normal dimensions were calculated according to the following equations22; expected normal LVIDd = 1.53 × (body weight)0.294 and expected normal LVIDs = 0.95 × (body weight)0.315. From the left apical 4-chamber view, pulsed Doppler was used to measure the peak early (E) and late (A) diastolic mitral inflow velocity, and tissue Doppler was used to measure the early diastolic (Ea) and late diastolic (Aa) velocity of the septal mitral annulus.

Statistical Analysis

Measurements are presented as the median and range. Variables were compared using the Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables (Fisher’s exact test for 2 categorical variables and the likelihood ratio test for more than 2 categorical variables). The relationships among different parameters were assessed by Spearman’s correlation analysis.

For the assessment of the comparative accuracy of different echocardiography variables in identifying patients with cardiac-related death, receiver operating characteristic (ROC) curves and the respective area under the ROC curve (AUC) were calculated for those variables with significance set at P < .01 in the Mann-Whitney U-test. Predictors of cardiac-related death within 1 year were assessed using binary logistic regression analysis. Echocardiographic variables with a P < .01 in univariate analyses were included in the multivariate model. Hosmer-Lemeshow statistics and accuracy rate were calculated to evaluate the fitness of the
Results

Table 1 shows the demographic data, physical examination results, and radiographic and echocardiographic characteristics of the study population. There were no significant differences between patients in Groups A and B with respect to age, sex, body weight, heart rate, and vertebral heart scale \((P > .05)\). The distribution of American College of Veterinary Internal Medicine classes between the 2 groups was significantly different \((P < .001)\).

The incidence of pulmonary edema was significantly higher in Group B \((58.3\%)\) than Group A \((7.7\%)\) \((P = .002)\). The use of angiotensin-converting enzyme (ACE) inhibitors \((P = .035)\), pimobendan \((P = .026)\), and loop diuretics \((P < .001)\) was significantly different between the 2 groups.

Results of conventional echocardiographic parameters are also shown in Table 1. There were significant differences in LA/Ao, LVIDd inc\%, E, E/A, and E/E\(_{m}\) between the 2 groups. Two of the 3 LA function parameters, LA-FAC\(_{total}\) \([37.1\% \text{ (20.7–55.7\%)} \text{ versus 50.1\% (35.5–64.7\%); } P = .001]\) and LA-FAC\(_{act}\) \([14.9\% \text{ (6.1–28.4\%)} \text{ versus 31.9\% (13.9–50.0\%); } P < .001]\), significantly decreased in Group B compared to Group A.

The LA function parameters were significantly related to some of the assessed conventional echocardiographic parameters (Fig 1). Significant correlations were found between LA-FAC\(_{total}\) and LA/Ao \((r = −0.535, P = .001)\), LVIDd inc\% \((r = −0.332, P = .042)\), LVIDs inc\% \((r = −0.577, P < .001)\), and \(A_{m}\) \((r = 0.532, P = .001)\) (Table 2). The LA-FAC\(_{act}\) had a significant correlation with age \((r = −0.330, P = .043)\), LA/Ao \((r = −0.771, P < .001)\), and LA-FAC\(_{act}\) \((r = 0.577, P < .001)\), and LA-FAC\(_{act}\) \((r = 0.532, P = .001)\) (Table 2).
$P < .001$, LVIDd inc% ($r = -0.562$, $P < .001$), LVIDs inc% ($r = -0.500$, $P = .001$), $E$ ($r = -0.551$, $P < .001$), $E/A$ ($r = -0.437$, $P = .006$), and $A_{m}$ ($r = 0.461$, $P = .004$) (Table 2).

For the comparative assessment of the accuracy of conventional echocardiographic parameters and LA function parameters in identifying the dogs with short survival times, ROC curves and the corresponding
Table 2. Correlates of left atrial function parameters.

<table>
<thead>
<tr>
<th>Variables</th>
<th>%LAEFtotal</th>
<th>%LAEFpass</th>
<th>%LAEFact</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. Value</td>
<td>r</td>
<td>P. Value</td>
<td>r</td>
</tr>
<tr>
<td>Age</td>
<td>.231</td>
<td>.932</td>
<td>.043</td>
</tr>
<tr>
<td>Body weight</td>
<td>.205</td>
<td>.264</td>
<td>.659</td>
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<tr>
<td>Heart rate</td>
<td>.530</td>
<td>.023</td>
<td>.378</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>.001</td>
<td>.0535</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVIDd inc%</td>
<td>.042</td>
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<td>.370</td>
</tr>
<tr>
<td>LVIDs inc%</td>
<td>&lt;.001</td>
<td>-.577</td>
<td>.140</td>
</tr>
<tr>
<td>FS</td>
<td>.064</td>
<td>.013</td>
<td>.408</td>
</tr>
<tr>
<td>E</td>
<td>.133</td>
<td>.069</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>E/A</td>
<td>.482</td>
<td>.976</td>
<td>.634</td>
</tr>
<tr>
<td>E/Ao</td>
<td>.136</td>
<td>.197</td>
<td>.006</td>
</tr>
<tr>
<td>A</td>
<td>.96</td>
<td>.389</td>
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</tr>
<tr>
<td>Am</td>
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<td>.532</td>
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<tr>
<td>%LAtotal</td>
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<td>.586</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>%LApass</td>
<td>&lt;.001</td>
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<tr>
<td>%LAfact</td>
<td>&lt;.001</td>
<td>.846</td>
<td>.401</td>
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A, late diastolic mitral inflow velocity; A_int, late diastolic velocity of the septal mitral annulus; E, peak early diastolic mitral inflow velocity; E_int, early diastolic velocity of the septal mitral annulus; FS, fractional shortening; LA/Ao, left atrial to aortic root ratio; LVIDd inc%, percent increase in left ventricular diameter in diastole; LVIDs inc%, percent increase in left ventricular diameter in systole; %LAEFact, left atrial active emptying fraction; %LAEFpass, left atrial passive emptying fraction; %LAEFtotal, left atrial total emptying fraction.

AUC were calculated. As shown in Table 3, the highest accuracy was obtained for LA-FACact, which had an AUC of 0.95, a sensitivity of 91%, and a specificity of 96%, followed by the LA/Ao, which had an AUC of 0.94, a sensitivity of 100%, and a specificity of 88%. The E/A had the lowest accuracy, with an AUC of 0.74, a sensitivity of 73%, and a specificity of 88%. Although the recent advancements in ultrasound equipment, such as tissue Doppler imaging and strain imaging, have facilitated more detailed analysis of cardiac ventricular function, assessment of LA size with LA/Ao using conventional B-mode remains one of the most important echocardiographic methods to evaluate the severity and prognosis of CMVHD. To the best of our knowledge, this study is the first report demonstrating that LA function analysis could be the most reliable prognostic indicator in dogs with CMVHD.

In our study, significant increases in LA/Ao were observed in nonsurvivor dogs, and the LA/Ao had a moderate and strong correlation with the reservoir and booster pump functions, respectively. However, LA enlargement does not always result in its functional incompetence. During chronic MR, the left atrium enlarges in size and the LA chamber becomes more compliant. Thus, the enlarged left atrium appears to exert an important compensatory mechanism by buffering the rise in pressure in the atrium and by

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC</th>
<th>95% CI</th>
<th>Se</th>
<th>Sp</th>
<th>Cutoff</th>
<th>P-Value</th>
</tr>
</thead>
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<tr>
<td>%LAEFact</td>
<td>0.74</td>
<td>.58–.91</td>
<td>.73</td>
<td>.72</td>
<td>1.36</td>
<td>.022</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>0.74</td>
<td>.58–.91</td>
<td>.73</td>
<td>.72</td>
<td>1.36</td>
<td>.022</td>
</tr>
<tr>
<td>E</td>
<td>0.74</td>
<td>.58–.91</td>
<td>.73</td>
<td>.72</td>
<td>1.36</td>
<td>.022</td>
</tr>
</tbody>
</table>

AUC, area under the receiver operating characteristic curve (AUC); LA/Ao, left atrial to aortic root ratio; E, peak early diastolic mitral inflow velocity; %LAEFact, left atrial total emptying fraction; LVIDd inc%, percent increase in left ventricular diameter in diastole; LVIDs inc%, percent increase in left ventricular diameter in systole; A, late diastolic mitral inflow velocity; Se, sensitivity; and Sp, specificity.

Many studies have reported the value of echocardiography for predicting survival time and providing prognostic indicators in dogs with CMVHD. Although the recent advancements in ultrasound equipment, such as tissue Doppler imaging and strain imaging, have facilitated more detailed analysis of cardiac ventricular function, assessment of LA size with LA/Ao using conventional B-mode remains one of the most important echocardiographic methods to evaluate the severity and prognosis of CMVHD.

### Table 4. Binary logistic regression analysis for cardiac-related death within 1 year.

<table>
<thead>
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<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA/Ao</td>
<td>0.956</td>
<td>0.929–0.984</td>
<td>.002</td>
</tr>
<tr>
<td>E</td>
<td>0.019</td>
<td>0.001–0.326</td>
<td>.006</td>
</tr>
<tr>
<td>%LAEFact</td>
<td>1.164</td>
<td>1.049–1.291</td>
<td>.004</td>
</tr>
<tr>
<td>%LAEFtotal</td>
<td>1.401</td>
<td>1.132–1.735</td>
<td>.002</td>
</tr>
</tbody>
</table>

CI, confidence interval; E, peak early diastolic mitral inflow velocity; LA/Ao, left atrial to aortic root ratio; OR, odds ratio; %LAEFact, left atrial active emptying fraction; %LAEFtotal, left atrial total emptying fraction.

### Discussion

The findings of this study indicate that LA size and function are strongly correlated with early death in dogs with CMVHD. Although several echocardiographic parameters were significantly different between the 2 groups, LA-FACact, the parameter corresponding to the booster pump function, was the most significant independent predictor of mortality in this study.

Based on the results of univariate analysis, the variables LA/Ao, E, LA-FACtotal, and LA-FACact were selected for multivariate logistic regression analysis (Table 4). In the multivariate logistic regression analysis, LA-FACact emerged as the only independent correlate of cardiac-related death within 1 year in our study population (odds ratio = 1.401; 95% confidence interval (CI), 1.132–1.735; P = .002) (Table 4).
providing an adequate ventricular filling volume. Moreover, it has been demonstrated that the Frank-Starling mechanism is also operative in the left atrium and that LA output increases as atrial volume increases, which contributes to maintaining a normal stroke volume.\textsuperscript{27} The increased atrial response to early-stage LV filling impairment is characterized by augmented reservoir and booster pump functions according to the Frank-Starling mechanism. At end-stage LV dysfunction, however, the atrial reservoir and the booster pump functions decline.\textsuperscript{28} Therefore, the analysis of atrial function, as well as its size, is required to evaluate the severity and prognosis of dogs with CMVHD.

During LV systole, pulmonary venous inflow distends the left atrium, which acts as a reservoir by storing energy in the form of pressure.\textsuperscript{29} The LA reservoir function is determined mainly by LA compliance (stiffness) and LV systolic function (systolic apical motion of the LV base facilitates LA filling) and, to a lesser extent, by right ventricular systole (pulmonary venous inflow).\textsuperscript{15,29} Decreased LA reservoir function has been described in human patients with severe MR.\textsuperscript{18} Similarly, this study showed that severe MR is associated with a significant reduction in LA reservoir function. This reduced function may be caused partly by reduced LV systolic function because %LVEF\textsubscript{total} had a mild correlation with the FS of the left ventricle in this study. However, the ultrastructural changes in the LA myocardium, including the presence of interstitial fibrosis and myocyte hypertrophy in patients with severe MR, may reduce LA compliance, resulting in reservoir dysfunction.\textsuperscript{30}

The LA functions as a conduit after the reservoir phase, allowing a passive transfer of blood from the pulmonary veins toward the left ventricle. The LA conduit function is determined mainly by LA elasticity and afterload. Although impaired LA conduit function was observed in human patients with severe MR,\textsuperscript{31} there was no difference between the conduit function of survivors and nonsurvivors in this study. The clinical utility of evaluating LA conduit function in dogs with CMVHD is still uncertain.

Active LA contraction, the booster pump function, finalizes LV filling during late diastole. It depends on LA afterload (LV compliance and end-diastolic filling pressure) and LA intrinsic contractility. In this study, impaired LA booster pump function was observed to a greater degree in nonsurvivor dogs, and it was the most significant independent predictor of mortality in this study; it may be related to the decreased LA contractility and increased LA afterload. These results are congruent with findings from human patients with hypertrophic cardiomyopathy and MR. In those studies, it was demonstrated that parameters of booster pump function had the highest correlation with the severity of the disease.\textsuperscript{16,30}

Mitral $A_m$ velocity with tissue Doppler imaging, another parameter of atrial function, had moderate correlations with LA-FAC\textsubscript{total} and LA-FAC\textsubscript{act} (reservoir and booster pump function, respectively). In humans, several studies have demonstrated that $A_m$ velocity can be used as a rapid and accurate marker of global atrial function.\textsuperscript{32,33} The $A_m$ velocity correlates with other parameters of atrial function, including the peak $A$ velocity, atrial ejection fraction, and atrial ejection force.\textsuperscript{33} Moreover, $A_m$ velocity has been shown to provide important prognostic information in patients with various cardiac diseases.\textsuperscript{34} In this study, there was no significant difference in $A_m$ velocity between the survivor and nonsurvivor dogs, reflecting a lower value for this prognostic predictor in dogs with CMVHD.

Some limitations of this study must be considered. First, no invasive assessment of LA mechanical properties or afterload was performed to prove the determinations of reduced LA function, which must be the focus of further specific studies. Second, the number of dogs studied was small, rendering the study underpowered to detect differences between groups. Last, it is possible that medication use influenced the echocardiographic parameters and survival time. The use of ACE inhibitors, pimobendan, and loop diuretics was significantly higher in the nonsurvivors. Because this study included dogs in various clinical stages, it was impossible to standardize the treatment.

In conclusion, both LA size and function are strongly correlated with the prognosis of dogs with CMVHD. Booster pump function was the most significant independent predictor of mortality in this study. The assessment of LA function can provide further insights about the pathophysiology and prognosis in dogs with CMVHD.

Footnotes
a Hitachi Medical Corp., Chiba, Japan
b IBM SPSS Statistics, version 21; IBM Corp., Chicago, IL

Acknowledgments

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References


